Remarks

Claims 1, 12, 14-18, 27, 40-44, 54 and 55 were pending in the application, with claims 27 and 40-44 being rejoined for examination. Claim 40 is hereby canceled. New claims 56-61 are added herein. No new matter is added. Therefore, after entry of this Amendment, **claims 1, 12, 14-18, 27, 41-44, and 54-61** are pending in this application. Consideration of the pending claims is requested.

Claims 1, 27, and 55 are amended herein. New claims 56-61 are added. Support for the claim amendments can be found throughout the specification, for instance:

Claim 1: page 5, lines 1-17; Figures 2, 12, 13, 15, and 17

Claim 27: page 5, lines 1-17; page 16, lines 12-18; page 30, line 5 to page 31, line 32; Figures 2, 12, 13, 15, and 17

Claim 56: page 16, lines 12-18; page 31, lines 23-32

Claims 57-60: page 2, lines 17-21; page 34, lines 24-29

Claim 61: page 5, lines 22-23

Applicants thank the Examiner for withdrawing many of the previous rejections. Applicants also thank the Examiner for rejoining claims 27 and 40-44 for examination.

Telephone Interview

Applicants thank Examiner Reddig for the courtesy of a telephone interview with their representatives, Susan W. Graf and Tanya M. Harding (of Klarquist Sparkman, LLP), and James Diehl (of Rigel Pharmaceuticals, Inc.) on March 7, 2008. During the telephone interview, the rejections under 35 U.S.C. § 112 were discussed. Potential claim amendments were discussed to address the § 112 rejections. Although complete agreement was not reached, Applicants believe that this amendment addresses the concerns that were discussed regarding the § 112 rejections. Applicants thank Examiner Reddig for agreeing to call their representatives to arrange for an additional interview when this response is received and before a new action is issued, if any concerns remain.

Claim Rejections – 35 U.S.C. § 112, second paragraph

Claims 1, 12, 14-18, 27, 40-44, 54, and 55 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants traverse to the extent that the rejections apply to the amended claims.

Claims 1, 12, and 14-18 are rejected as allegedly indefinite because it is asserted that it is unclear whether the angiogenesis polypeptide of the cell-based assay of claim 1 is the same angiogenesis polypeptide of the kinase assay. Claims 1 and 55 are amended herein to replace references to an "angiogenesis polypeptide" with "Axl polypeptide." Claim 1 is also amended to replace "*the* angiogenesis polypeptide" in line 9 of claim 1 with "*said* Axl polypeptide."

Claim 1 is also rejected as allegedly indefinite because it is asserted that it is unclear as to what inhibition in the *in vitro* kinase activity of claim 1 is. Claim 1 is amended herein to recite "inhibition of the *in vitro* kinase activity of the Axl polypeptide . . ."

Claims 1 and 27 are further rejected as allegedly indefinite because it is asserted that they do not require that the endothelial cell have an angiogenesis phenotype. Though Applicants do not agree that the claims are indefinite with regard to the endothelial cell, claims 1 and 27 are amended to recite a cell-based assay, "which assay produces an angiogenesis phenotype in said endothelial cell in the absence of the compound . . .". This amendment reflects that the methods for assessing a cell-based angiogenesis phenotype are carried out under conditions that produce the angiogenesis phenotype in the endothelial cells used. For example, in order to perform a haptotaxis assay, endothelial cells are cultured under conditions that produce the haptotaxis phenotype, such as in the presence of a fibronectin or vitronection gradient (Figures 2, 12, 13, and 15). Similarly, in the tube formation assay, endothelial cells are cultured under conditions that promote tube formation, such as co-culture with pulmonary artery smooth muscle cells (Figure 17). Additional support for this amendment may be found in the specification, for instance at page 5, lines 1-17.

Based on the forgoing arguments and amendments to the claims, Applicants request withdrawal of these rejections under 35 U.S.C. § 112, second paragraph.

Claim Rejections – 35 U.S.C. § 112, first paragraph

Claims 1, 12, 14-18, 27, 40-44, 54, and 55 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement and written description requirements. Each rejection is discussed separately below, with reference to the sections as numbered in the Office action.

Enablement

Section 7

Claims 1, 12, 14-18, 27, 40-44, 54, and 55 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants traverse to the extent that the rejections apply to the amended claims.

First, the Office action asserts that "[g]iven that activation of Axl inhibits angiogenesis *and Applicants argue as such*, one of skill in the art would not believe it more likely than not the identification of compounds that inhibit Axl kinase activity or down-regulate Axl would lead to the identification of compounds that inhibit angiogenesis" (Office action, page 6, first paragraph, emphasis added). The Office action also cites Gallicchio *et al.*, *Blood* 105:1970-1976, 2005 as teaching that activation of Axl by Gas-6 activates Axl and inhibits VEGF-dependent angiogenesis (Office action, page 5, last paragraph). Applicants respectfully point out that this reference is from 2005, well after the October 29, 2003 filing date of the instant application. Therefore, this reference is not relevant to the determination as to whether the specification is enabling, a determination that is made *at the time of filing*.

However, Applicants *do not* argue that activation of Axl inhibits angiogenesis; rather, they argue the opposite. In the amendment filed on October 5, 2007 (page 11, third full paragraph), Applicants point out that the claims are directed to identifying a compound that ***inhibits*** *Axl and* ***inhibits*** *an angiogenesis phenotype assay* in an endothelial cell comprising Axl

polypeptide. This is clearly shown in the specification in Figures 11-15 and 17, which show that an inhibitor of Axl (RNAi directed to Axl) inhibits haptotaxis, proliferation, β1 integrin expression, and tube formation in HUVEC cells. Therefore, based on the teaching of the instant application, one of skill in the art would believe it more likely than not that the identification of compounds that inhibit Axl would lead to the identification of compounds that inhibit angiogenesis.

The Office action further asserts that the claims are not enabled because of the alleged unpredictability of extrapolating the results of *in vitro* drug assays to *in vivo* responses. The Office action contends that the specification provides insufficient guidance and no working examples which would allow one of skill to predict that the invention would function as claimed with a reasonable expectation of success. Applicants request reconsideration in light of the enclosed Declaration under 37 C.F.R. §1.132 signed by Dr. Sacha Holland.

As shown in the Declaration of Dr. Holland ("Declaration"), compounds were identified *in vitro* as inhibitors of angiogenesis utilizing cell-based assays such as cell proliferation, haptotaxis, and tube formation in endothelial cells and Axl kinase activity in HeLa cells (Declaration, paragraph 4). These compounds have been shown to inhibit angiogenesis in *in vivo* assays, such as the mouse sponge angiogenesis assay, tumor xenograft assay, and mouse corneal assay. These assays are discussed in the specification, for instance at page 5, lines 17-19 and Figure 18 (sponge angiogenesis assay); page 33, lines 27-31 and page 49, lines 1-20 (tumor xenograft assay); and page 33, lines 23-26 (mouse corneal assay).

The Declaration indicates that an Axl short hairpin RNA (shRNA) which down-regulates Axl expression (and thus necessarily kinase activity) in endothelial cells *in vitro* inhibits angiogenesis *in vivo* in a mouse sponge angiogenesis assay, as demonstrated by decreased human Tie-2 expression (a marker of human endothelial cells), decreased implant perfusion, and formation of smaller vessels lacking patent lumens as compared to controls (Declaration, paragraph 6). In addition, the Axl shRNA impaired the ability of the breast tumor cell line MDA-MB-231 to grow as a xenograft in SCID mice compared to controls (Declaration, paragraph 7). Small molecule Axl kinase inhibitors decreased basic fibroblast growth factor-

induced neovascularization in a mouse corneal pocket assay (Declaration, paragraph 8) and also decreased growth of tumor cell lines in mouse xenograft assays (Declaration, paragraph 9). These data demonstrate that compounds identified using the claimed cell-based *in vitro* screening methods inhibit angiogenesis *in vivo*.

Based on the foregoing, Applicants assert that the claimed methods are enabled by the specification. Therefore, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

Section 8

Claims 1, 12, 14-18, and 55 are further rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. The Office action alleges that the specification does not provide enablement for methods of identifying a compound that inhibits angiogenesis in which the Axl polypeptide comprises an amino acid sequence with greater than 95% identity to SEQ ID NO: 4. Applicants traverse and request reconsideration.

Axl is a receptor tyrosine kinase that is stimulated by the secreted protein Gas6 (growth arrest specific 6) which was well known at the time of filing of the instant application (O'Bryan *et al.*, *Mol. Cell. Biol.* 11:5016-5031, 1991; submitted herewith as **Exhibit B**; Stitt *et al.*, *Cell* 80:664-670, 1995; Abstract submitted herewith as **Exhibit C**). Axl contains an extracellular ligand-binding region with two immunoglobulin-like (IgL) domains followed by two fibronectin type III (FNIII) repeats, a transmembrane segment, an intracellular tyrosine kinase domain, and two potential phosphatidylinositol 3-kinase binding sites (O'Bryan, page 5019, right column). Each of these domains was well known at the time of the identification of Axl; O'Bryan *et al.* provides alignments and identifies conserved residues and/or consensus sequences for the IgL, FNIII, transmembrane, and tyrosine kinase domains (Figure 3). In addition, those residues critical to kinase activity and methods for testing a polypeptide for kinase activity were well known to one of skill in the art at the time of filing. For example, O'Bryan *et al.* initially identified Axl as a receptor tyrosine kinase based on the presence of homology to known kinases (page 5019, paragraph bridging left and right columns) and by anti-phosphotyrosine Western blotting (page 5021 and Figure 7). Further, Hanks and Hunter (*FASEB J.* 9:576-596, 1995;

submitted herewith as **Exhibit D**) provide a detailed analysis of conserved features of protein kinases, including tyrosine kinases.

The specification provides a representative Axl polypeptide sequence (SEQ ID NO: 4). Further, the specification provides methods for creating alignments and determining sequence identity at page 11, line 15 to page 13, line 11. Based on the specification, at the time of filing, one of ordinary skill could make and use polypeptides having greater than 95% identity to SEQ ID NO: 4 which retain kinase activity in the absence of a test compound.

The Office action asserts that "screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed. Cir. 2004) that screening assays are not sufficient to enable an invention because they are a mere wish or plan for obtaining the claimed chemical invention" (Office action page 12, third full paragraph). However, the cited case does not discuss enablement, but is directed solely to the written description requirement. In *Rochester*, the Federal Circuit stated "an adequate written description of a DNA . . . 'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention" (*University of Rochester v. G.D. Searle & Co., Inc.* 358 F.3d 916, 69 USPQ2d 1886, 1895 (Fed. Cir. 2004); emphasis added, internal citations removed).

The claims at issue in *Rochester* were directed to methods for inhibiting PGHS-2 activity in a human by administering a compound that selectively inhibits the enzyme activity (69 USPQ2d at 1888-1889). In that case, the claimed methods required use of a compound not yet identified by Rochester. In contrast, the pending claims in this application relate to a method for identifying a compound that inhibits angiogenesis. The holding of *Rochester* was that because the patent at issue did not provide "compounds that can be used to carry out the claimed methods – *an essential element of every claim* of that patent . . ." the specification did not provide an adequate written description (69 USPQ2d at 1897, emphasis added). However, in this application, the claims are directed to a method of *identifying* a compound; the compound itself is not used to carry out the claimed methods. Therefore, even if *Rochester* were applicable to the question of enablement, its holding is inapposite in this situation.

The proper test for enablement is whether undue experimentation is required (*In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). As described in *Wands*, "a considerable amount of experimentation is permissible, if it is merely routine..." (*Wands*, 8 USPQ2d at 1404). Based on the state of the art at the time of the filing of the instant application, it would have required only routine experimentation for one of skill in the art to make and use polypeptides having greater than 95% identity to SEQ ID NO: 4 having kinase activity in the absence of a test compound. For example, O'Bryan *et al.* provides an alignment of the Axl polypeptide tyrosine kinase domain and ten other receptor tyrosine kinases (Figure 3C, page 5023), identifying conserved residues and a consensus sequence. Further, the structure and function of receptor tyrosine kinases, as well as methods to assay kinase activity, were well known at the time of filing of the instant application (see *e.g.*, Hanks and Hunter, **Exhibit D**). Therefore, one of skill in the art is enabled by the specification, which provides an exemplary Axl sequence (SEQ ID NO: 4) and algorithms to determine sequence identity, to make and use Axl polypeptides having greater than 95% identity to SEQ ID NO: 4 having kinase activity.

Based on the foregoing discussion, Applicants assert that the claimed methods are enabled by the specification. Therefore, Applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

Section 9

Claims 27, 40-44, and 54 are rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking enablement. Specifically, the Office action asserts that "no nexus has been established between the broadly claimed Axl polypeptide, the down regulation of said polypeptide, and inhibiting angiogenesis because the unpredictability of protein biochemistry is well known in the art" (Office action, page 16, first full paragraph). Applicants traverse to the extent that the rejections apply to the amended claims.

Claim 27 is amended herein to recite "an amino acid sequence with greater than 95% identity to full length SEQ ID NO: 4 wherein the Axl polypeptide has kinase activity in the absence of said compound..." As discussed above with relation to the enablement rejection in

Section 8 of the Office action, the specification provides an Axl polypeptide sequence (SEQ ID NO: 4) and methods for determining sequence identity (*e.g.* at page 11, line 15 to page 13, line 11). In addition, those residues critical to kinase activity and methods for testing a polypeptide for kinase activity would have been well known to one of skill in the art at the time of filing. Based on this, one of ordinary skill could make and use polypeptides having greater than 95% identity to SEQ ID NO: 4 which retain kinase activity in the absence of a test compound in the claimed methods.

Claim 27 is further amended to recite "performing a cell-based assay, which assay produces an angiogenesis phenotype in said endothelial cell in the absence of the compound, wherein inhibition of the angiogenesis phenotype" identifies a compound as an inhibitor of angiogenesis. The § 112 rejection of claim 27 appears to assert that no nexus has been established between angiogenesis and functional effects on Axl polypeptide beyond down regulation of SEQ ID NO: 4 (Office action, page 17, first full paragraph). The specification teaches cell-based assays for an angiogenesis phenotype in endothelial cells, such as haptotaxis, integrin expression, cell proliferation, and endothelial tube formation (see *e.g.* page 31, line 23 to page 33, line12). The nexus between these assays and angiogenesis is well known in the art. Figures 11-13, 15, and 17 show examples of determining inhibition of an angiogenesis phenotype, such as haptotaxis (Figures 11-13 and 15), cell proliferation (Figure 15), β1 integrin expression (Figure 12), and tube formation (Figure 17). The Declaration under 37 C.F.R. § 1.132 of Dr. Sacha Holland submitted herewith further provides support for the nexus between a cell-based angiogenesis phenotype and *in vivo* inhibition of angiogenesis (Declaration, paragraphs 8 and 9). This data is also discussed above in the section addressing the enablement rejection of Section 7 of the Office action.

The Office action also cites references which allegedly teach the unpredictability of identifying anticancer agents that are effective tumor drugs in patients (Office action, pages 17-18). Applicants respectfully point out that the claims are drawn to methods of identifying compounds that inhibit angiogenesis, not methods of identifying anti-tumor drugs that are successful in the clinical setting. The instant specification enables methods of identifying inhibitors of angiogenesis, as discussed above.

Based on the foregoing discussion and the amendments to claim 27, Applicants request the withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

Written Description

Section 10

Claims 1, 12, 14-18, 27, 40-44, 54, and 55 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking an adequate written description in the specification. Specifically, the Office action asserts that the specification does not adequately describe "the complete structure of the Axl/angiogenesis polypeptide with greater than 95% identity to SEQ ID NO: 4 that is useful for identifying a compound that inhibits angiogenesis, nor does the specification provide any partial structure . . . nor any physical or chemical characteristics . . . nor any functional characteristics coupled with a known or disclosed correlation between structure and function." Office action, paragraph bridging pages 23-24. Applicants traverse to the extent that the rejections apply to the amended claims.

As established in *Ex parte Parks*, "adequate description under the first paragraph of 35 U.S.C. 112 does not require literal support for the claimed invention. . . . Rather, it is sufficient if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an appellant had possession of the concept of what is claimed" *Ex parte Parks,* 30 USPQ2d 1234, 1236-37 (B.P.A.I. 1993) (emphasis added). Moreover, the M.P.E.P. at § 2163 states that "[w]hat is conventional or well known to one of skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d at 1384, 231 USPQ at 94 . . . If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g. *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson,* 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient")."

Claim 1 and claim 27 (as amended herein) recite an Axl polypeptide comprising "an amino acid sequence with greater than 95% identity to full length SEQ ID NO: 4 wherein the

Axl polypeptide has kinase activity . . .". The Axl polypeptide utilized in the claimed methods also functions in an angiogenesis assay, such as inhibition of an angiogenesis phenotype in an endothelial cell-based assay. The instant application therefore provides a complete structure (SEQ ID NO: 4) and functional characteristics (*i.e.* kinase activity and function in an angiogenesis assay) that describe an Axl polypeptide that is useful for identifying a compound that inhibits angiogenesis. The specification also teaches that Axl is a receptor tyrosine kinase that is activated by the ligand Gas6 (page 6, lines 8-11). As discussed above with reference to the enablement rejection under paragraph 8, Axl polypeptide was also well known at the time of filing of the instant application, including the tyrosine kinase domain (see *e.g.* O'Bryan *et al.*, Figure 3C). One of skill in the art would recognize the conserved residues required to maintain kinase activity and methods to assay kinase activity. Further, the specification provides methods for creating sequence alignments and determining sequence identity at page 11, line 15 to page 13, line 11. The specification also describes "conservatively modified variants" which include conservative amino acid substitutions, as well as polymorphic variants, homologs, and alleles (page 15, lines 11-24).

Based on the above, one of ordinary skill in the art would have recognized that at the time of filing, Applicants had possession of the claimed subject matter, including polypeptides that share structural and functional features with SEQ ID NO: 4. Therefore, Applicants request that this rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

Section 11

Claims 1, 12, 14-18, 27, 40-44, 54, and 55 are rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking an adequate written description in the specification. Specifically, the Office action asserts that "there is nothing in the specification to suggest the specific combination of assay steps in claim 1 to identify a compound that inhibits angiogenesis" (Office action page 28, first paragraph). Applicants traverse.

As established in *Ex parte Parks*, "adequate description under the first paragraph of 35 U.S.C. 112 does not require literal support for the claimed invention. . . . Rather, it is sufficient if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an

appellant had possession of the concept of what is claimed" *Ex parte Parks,* 30 USPQ2d 1234, 1236-37 (B.P.A.I. 1993) (emphasis added). Moreover, the M.P.E.P. at §2163 states that "[w]hat is conventional or well known to one of skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d at 1384, 231 USPQ at 94 . . . If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g. *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson,* 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient")."

The specification describes methods for identifying a compound that inhibits angiogenesis comprising contacting the compound with an Axl polypeptide and determining the functional effect of the compound on the polypeptide (page 2, lines 23-33). Determining the functional effect includes "assaying for a compound that increases or decreases a parameter that is indirectly or directly under the influence of an angiogenesis peptide" and includes enzymatic activity and cell-based angiogenesis phenotypes (including cell proliferation, cell surface marker expression, haptotaxis, and tube formation) (page 8, line 27 to page 9, line 8). Further, assays for identifying modulators of angiogenesis proteins are described on page 30, lines 5-29. The specification states that "any suitable physical, chemical, or phenotypic change that affects activity or binding can be used to assess the influence of a test compound on the polypeptide of this invention" (page 30, lines 20-22). There is no suggestion that only one of the described assays may be used to identify an inhibitor of angiogenesis. Based on the specification, one of skill in the art would understand that a combination of the described assays may be desirable in identifying a compound that inhibits angiogenesis. In fact, the specification shows examples of the use of a combination of assays in Figure 13 (effect of Axl RNAi on haptotaxis and β1 integrin expression) and Figure 15 (haptotaxis and cell proliferation).

The specification describes both *in vitro* (both test-tube and cell-based) kinase assays and cell-based angiogenesis phenotype assays. Further, the specification describes the use of combinations of other assays. One of skill in the art would readily recognize from the specification that any combination of the described assays could be used in methods for

identifying compounds that inhibit angiogenesis. Therefore, claim 1 is adequately supported by the specification.

In addition, the rejection asserts that there is no support in the claims or specification as originally filed to support "an Axl polypeptide comprising SEQ ID NO: 4, which encompasses sequences outside of SEQ ID NO: 4" (Office action, page 28, first full paragraph). Applicants traverse. The specification describes labels which may be incorporated into a protein (page 16, lines 6-11) and fusion proteins (page 16, lines 24-26 and page 27, lines 20-25). Therefore, there is support in the specification for an Axl polypeptide which comprises SEQ ID NO: 4 and additional elements.

Based on the foregoing discussion, Applicants request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

Conclusion

Applicants respectfully submit that the claims are now in condition for allowance. If any issues remain, the Examiner is requested to contact the undersigned to arrange a telephonic interview prior to the preparation of any further written action.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

By /Susan W. Graf/
Susan W. Graf, Ph.D.
Registration No. 60,432